The ADMINISTRATION of ANTIPYRETICS in TYPHOID FEVER.

by

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During the past eight years I have had under my care a more or less continuous succession of cases of typhoid fever: sometimes the cases were few in number at others instances of the disease were more frequent, being almost epidemic. That it never assumed epidemic proportions was due to there being no common infecting cause and that it lingered all those years was owing to defective sanitary conditions in various sections of the community. These defective sanitary conditions are being gradually improved and typhoid is now much less common.

However, my object in this paper is not to discuss the relation of typhoid fever towards sanitary or insanitary conditions, but a desire to submit for your consideration the results of a method of treatment I have adopted in typhoid during the past six years; not that there is anything new in the remedy used, but rather that the remedy - if it may be so called in those days of more accurate therapeutics - has been used systematically to attain certain objects and to effect certain desired purposes in the course of the fever.

So far as the present treatment of typhoid is concerned one of three methods or a combination of any of them is usually adopted.

1. The expectant, which is in a manner negative, so far as direct antagonism to the fever is concerned.

2. The antiseptic, which by the introduction of germicides, aims at the destruction of the infection and cause of the fever within the intestine.

3. The antipyretic which aims at a reduction of the temperature by so controlling the causes of pyrexia, as to reduce the risk of complications and to mitigate the course and nature of the disease.

In judging of the merits of these various forms of treatment it is no easy matter to decide which is the best, each has its advocates and one who has long used a certain form of treatment will have acquired more skill in its use than those practising it for the first time, and there are so many types of the disease some mild others severe and varying from year to year. Again the social conditions under which typhoid occurs must have an influence in determining the result and course of the disease by the treatment that can be carried out, the opportunities for a successful treatment in hospitals and the houses of the well-to-do being far in advance of those in the homes of the working class,

where overcrowding is common, improper cooking a rule and rest difficult to secure. Frequently too in small towns and petty burghs the sanitary arrangements are very imperfect, there is a lack of hospital accommodation of homes permitting isolation and of skilled nursing: now all those conditions of type, locality and nursing will have an influence in determining the value of any form of treatment.

In the report of cases I am about to submit to your notice the patients were all, or nearly all members of a mining community and being without hospital accommodation they had to be treated in their own homes: generally the houses were of two compartments and it was rarely possible to isolate the patients or secure the rest and quiet so essential to their well-being. The most elementary knowledge of sickroom attendance and cooking was often wanting besides the difficulty with those so little accustomed to sicknursing of making them understand the peculiar significance of diet to a typhoid patient.

Previous to June 1893 I treated all typhoid patients according to the symptoms manifested: if the temperature was high I used an anitpyretic either in large doses or in small doses frequently repeated, and always in such a way, that so far as I was able, I

made sure the temperature would fall. Other symptoms were treated by the exhibition of appropriate remedies and this I still continue, only there is this difference that with an alteration in the manner of administering antipyretics complications are much less frequent and the rate of mortality decreased. What seems a great drawback in the administration of antipyretics, and I refer to phenacetin, antipyrin, antifebrin and drugs of that series, is the sudden drop of temperature, a drop so sudden as in some patients to occasion a degree of shock with a tendency towards collapse. Binz, Cash, Brunton and others have shewn that the antipyretic acts by causing contraction of the protoplasm within the cell membrane so limiting the extent of protoplasmic surface exposed to oxidation and heat production: the antipyretic doing this, either by direct action on the cell or by stimulating the heat centres in the brain and spinal cord. Lister has observed that while the cell protoplasm is comparatively contracted in health it is much diffused in inflammation and in fever, hence anything that suddenly stimulates the protoplasm to abnormal contraction will cause a rapid arrest of oxidation and of heat development. Now, the blood in the course of circulation is the great heat carrier and heat distributer and if

suddenly there is a great reduction in the amount of heat manufactured there will be a sudden change of temperature in the blood reaching the heart. Brunton has also shewn that warm blood stimulates the heart, but that a sudden reduction of temperature cools the blood and so to speak chills and weakens the heart. This may explain why the use of antiypretics is viewed with a certain mistrust in the treatment of fevers: yet the general rule is to treat a high temperature with an antipyretic in large doses or what is much the same thing with small doses frequently repeated. Sometimes it is dissolved and administered in soluble form so that it is at once absorbed causing immediate restriction of oxidation, a quick fall of temperature with a degree of shock to the heart and consequent enfeeblement. Then for some time no more antipyretic is given and in a strong patient this effect soon wears off, but the temperature rises again and with a worse result - action and reaction are always equal and opposite - and while it is true antipyretics have little power to lower the temperature in health or make it fall below normal in disease, still so administered they produce shock, which will be followed by reaction, and to that degree is harm done to the patient.

When the temperature is again high a similar dose is given and in a similar manner with another shock to the heart, and this goes on irregularly in the course of the fever as the temperature seems to indicate till the feeble pulse gives a warning of heart failure: and as antipyretics have little, if any, influence on the duration of the disease their administration in this way saps the strength of the patient long before its course has run.

It is maintained that in fevers high temperature of itself is not injurious, but is on the contrary a useful reaction against the invading microbes and tending towards their ultimate destruction; still it is a reaction calling for careful guidance and regulation because this does not appear to be the only effect of high temperature; another and more immediate result is that it causes expansion of cell protoplasm and permits a readier absorption of toxines. It is also stated that at comparatively low temperatures many organisms flourish most, while the best temperature for bacillus typhosus is only slightly above the normal. Clinically, to every practitioner the temperature is the great guide as to the progress of the case, if it is very high rising to 105° and 106° F., he knows he must reduce it if the patient is to live and

that if he succeeds he averts an imminent danger: further, despite the fact of bacillus typhosus flourishing most at or near normal temperature we know if the temperature is only normal and remains normal the patient is well. We are much in the dark as to the manner of action of bacilli, but we know that with certain varieties their virulence varies with their environment, that under one set of conditions they may be comparatively harmless while under others they will manufacture toxines actively poisonous. For instance, the bacillus coli is present though harmless under normal conditions but multiplies and become virulent in typhoid and other intestinal conditions where the gut undergoes morbid change: not only from being harmless does it become virulent but in typhoid its products appear to intensify the virulence of the specific infection. Dieulafoy has shown that a slight change of conditions, such as effete products being increased or pent up, may make a great difference in pathogenic activity and the nature of the toxines secreted; and it is highly probable that on the amount and character of the toxines absorbed into and retained in the system will depend the clemency or malignancy of the disease and the more we eliminate effete products the less virulent will be the toxine produced.

As before said the temperature is our chief guide as to the virulence or otherwise of the disease, and a falling temperature in a typhoid patient, free from complications, means that the patient is progressing favourably and it will make no difference whether the falling temperature takes place naturally or is induced artificially provided the process involves no destruction or sapping of the vital powers of the patient.

It may be said that if simple reduction of temperature is a remedy the cure of typhoid is easy but that is not so, generally by the time typhoid is diagnosed pathological changes have taken place, and irrespective of the life history of the organism there will be the characteristic inflammation and may be ulceration of Peyer's patches and solitary glands, which would require careful treatment for days or weeks, before healing can be established. Still, in a small percentage of cases a crisis does occur, the patient has a good sweat, the temperature falls and the disease aborts; this only happens in the earliest stage before there is any pathological lesion. There may be a doubt as to whether it is the organism or its toxines or both that is the immediate cause of the high temperature, but clinically there is no doubt

that a very high temperature quickly kills and that a high temperature long maintained makes every typhoid case grave. The rising temperature may be the apparent indication of an increased absorption of toxines, but it seems highly probable that the higher the temperature the more active the tissue change and the quicker the absorption; so that temperature is not a mere symptom but a factor in the severity of the disease and any judicious reduction of temperature is a beneficial form of treatment. This is every day practise and seems to coincide with the observations of Lister that in fevers, i.e., high temperatures, the cell protoplasm is more diffused and consequently more absorbent, so that anything contracting the cell protoplasm will not only retard oxidation and lower the temperature but will restrict the power of absorption.

Antipyretics such as phenacetin, antipyrin and antifebrin have been discovered to act in this way so that they have that power for good, but besides this power for good all of them have considerable power for harm if injudiciously given. If they are administered in large doses or in small doses too frequently repeated the result is a diminished vitality limiting their further use and without having gained any lasting

control of the temperature.

Antipyrin is usually given in doses of from 10 to 15 grains though sometimes as much as 30 grains is given at once, repeated in an hour and followed in another hour, by another 15 grains: it is readily soluble, quickly absorbed and there is a sudden fall of temperature not infrequently with cold clammy sweats and cyanosis so that its administration could never be safely maintained throughout the course of the disease. What seemed to take place was a sudden transient reduction of temperature with a weakened heart's action and no beneficial modification in the course of the fever. Now, in the treatment of typhoid fever by controlling the temperature we must try to do so without unduly depressing the heart and at the same time aim at the elimination of effete matters and any poisonous products that are being manufactured. If we secure these aims we will not only control and lower the temperature, but we will diminish the virulence of the toxine, restrict accumulation and make the whole aspect of the case more favourable; there will be less likelihood of complications and a smaller death rate. Of antifebrin and thallin I have little experience, though in one patient where the former was prescribed every four

hours, there was smoky urine with every evidence of altered constitution of the blood, however, my experience of this medicine is too limited to do more than mention it though I am aware that with many it enjoys a good reputation.

Phenacetin on the other hand I have used continuously during the past six years, using it not only in the treatment of typhoid but in the early stages of other diseases where temperature is a symptom. It is readily soluble in alcohol, insoluble in acids except sulphuric, and only very sparingly soluble in water. It is often used in the early stages of fever being usually prescribed in doses of from 5 to 10 grains every two or three hours. Often too, it is dissolved in alcohol so that it may be readily absorbed; given in either of those ways it acts in the same manner as antipyrin, the temperature falls, but it falls sharply and suddenly causing depression. Even in 5 grain doses, undissolved and given every 4 hours it will in the course of two or three days cause considerable feebleness, though in the same dose and given in the same way, but at longer intervals a beneficial result is secured with little risk of harm.

In adults the maximum dose was 5 grains every 8 hours, floated on water or put on the tongue and

washed over with water. Giving it in this way its administration was continued during practically the entire course of the fever and there was no instance in which there was harmful depression: the temperature fell more or less without requiring larger doses or a more frequent repetition. That was the maximum dose and it was given for weeks if necessary but always until the temperature fell to 101° F., or below, then the dose was diminished or not given so often. But while 5 grains every 8 hours was the maximum dose smaller doses were given to children or persons where there seemed any risk of cardiac failure, and if any important complication arose - which was seldom - its administration was stopped and the complication treated with the remedy indicated. While there was no instance in which harm was done from an undue depression still such small doses and given at such long intervals necessitates careful attention to pulse and temperature that there may be no injurious influence. Clinically the advantages seem to be that owing to the drug being so slightly soluble, it is slowly absorbed there is a gradual instead of a sudden reduction of temperature without depression, and being given at such long intervals all the drug is absorbed before another dose is taken and patients do not

exhibit toxic symptoms in the course of treatment as has been found but bear it well during the entire period. Another advantage and probably the chief one is the very free way in which the patient perspires, all of them perspiring freely many of them copiously and without being harmfully weakened: so far from the perspiration producing any bad effect I gathered the impression that patients who did not perspire readily with this treatment were apt to be of a malignant type and they are generally cases in which the disease was well run before treatment was started. This free perspiration seems not only a valuable aid in the direct reduction of temperature but also seems to be of great value in the elimination of effete matters. I can well remember the loathsome aspect and condition of many of my typhoid patients previous to treating them in this way, but during the past six years such cases may well be said to have been characterised by their absence. There is little or no delirium or only at the earliest stages, instead of being as it often was, a common symptom winding up with that dull, low, half-inaminate muttering so frequent as a closing scene. Headache and restlessness are much diminished and the tongue soon becomes red and moist round the tip and edges with a thin

covering of white fur over the back and middle instead of being parched, glazed and ridged with lips open and teeth brown with accumulated sordes.

Diarrhoea was frequent but seldom of long duration: if it lasted long and was profuse I was afraid for haemorrhage or perforation and in more than one instance one or both happened.

Abdominal distention was rarely extreme though often present.

Haemorrhage was the most frequent complication; in some of the cases it was very severe and led to a fatal result.

Perforation also happened and was always fatal; other complications were rare.

It must not be understood that phenacetin was the only remedy used, though it was the only one unless some complication ensued. Towards the termination of the disease a moderate use of stimulants was prescribed but seldom exceeding two ounces in twenty-four hours, and it was only given if indicated by the pulse. Diarrhoea was restrained by suitable diet astringents and opiates.

Haemorrhage was controlled with the icebag, turpentine or a full dose of opium, and in every case the diet was restricted to fluids; milk, egg flip, soups

and diluents.

From June 1893 to June 1899 I treated 82 cases in this way and the years of occurrence were from June of 1893- 5 cases; 1894, 18 cases; 1895, 27 cases; 1896, 19 cases; 1897, 4 cases; 1898, 8 cases and to June of 1899, 1 case. These cases were all or nearly all in the worst houses of the crowded homes of miners and extending as they do over a period of six years it is probable the disease occurred in all its usual types. Showing the readiness with which it will spread in a household, 61 cases occurred in families where more than one member suffered from the disease; in the remaining 21 instances only one person was affected. Of the 82 cases 76 recovered and 6 were fatal giving a percentage mortality of 7·4. Of the 76 recoveries 3 cases were abortive the duration being under 14 days: in 14 cases the duration was 14 days and less than 21: in 12 cases it was 21 days and less than 28: in 22 cases it was 28 and less than 35: in 16 cases it was 35 days and less than 42: in 3 cases it was 42 days and less than 49: in 3 cases it was 49 and less than 56 and in other 3 cases it was 56 days or more.

The average duration of cases ending in recovery was 29 days so that the treatment did not modify the

duration of the disease though it regulated the temperature, provided for excretion and mitigated the severity.

Of the 6 fatal cases 1 died from penumonia: 2 from excessive haemorrhage and 3 from perforation with peritonitis and the average duration of a case ending fatally was 17 days.

Osler gives the usual mortality as ranging from 10 to 30 per cent: Murchison as 17·45: Bristowe 15 to 16: Brand by hydrotherapy has a mortality of 7·8 and the present rate at Charing Cross Hospital by the expectant method is 18·5.

I quite recognise the doubt that enshrouds statistics and that 82 cases bulk small in the consideration of a treatment for typhoid but these 82 cases extended over a period of six years and the mortality of 7·4 was obtained under by no means favourable conditions.

I append a list with the name, residence, duration and result obtaining in each case.

	Name	Residence	Duration	Result.
1.	Jane Bowman	10 Union st.	32 days	Recovered
2.	Janet Bowman	10 "	25 "	"
3.	Betsy "	"	16 "	"
4.	John Beveridge	17 School st.	29 "	"
5.	James "	"	56 "	"
6.	Andrew "	"	31 "	"
7.	Wm. McAndrew	19 Broad st.	16 "	"
8.	John Russell	27 School st.	61 "	"
9.	Mary Gordon	22 "	37 "	"
10.	James "	"	57 "	"
11.	Grace Paton	174 High st.	57 "	"
12.	Andrew Hunter	114 High st.	36 "	"
13.	John "	"	13 "	"
14.	James Sheddon	101 High st.	51 "	"
15.	James " Jr.	"	7 "	"
16.	Mary Watson	6 School st.	28 "	"
17.	Lizzie Bain	11 "	35 "	"
18.	Alex. "	"	36 "	"
19.	Thomas "	"	41 "	"
20.	Betsy McGuire	43 Bridge st.	20 "	"
21.	Helen Bowman	45 Bridge st.	31 "	"
22.	Thos. Raeburn	Union st.	38 "	"
23.	Jas. Drysdale	31 Bridge st.	31 "	"

	Name	Residence	Duration	Result.
24.	K. Leitch	50 Foulford rd.	31 days	Recovered
25.	Robt.Bowman	18 Thistle st.	16 "	"
26.	Wm.Bowman	18 "	37 "	"
27.	Jane "	"	26 "	"
28.	Chas.Mellon	33 Bridge st.	25 "	"
29.	Mary "	"	32 "	"
30.	Mrs "	"	31 "	"
31.	Wm. "	"	28 "	"
32.	Ed. "	"	35 "	"
33.	John Duncan	216 High st.	24 "	"
34.	Helen Beveridge	20 Bridge st.	12 "	"
35.	Maggie "	"	40 "	"
36.	David "	48 "	48 "	"
37.	John Cook	4 Thistle st.	14 "	"
38.	Robert "	"	48 "	"
39.	Mrs Cook	"	23 "	"
40.	Arch. "	"	7 "	Died
41.	Wm. "	"	12 "	Died
42.	Annie "	"	36 "	Recovered
43.	Margt.Beattie	19 School st.	23 "	"
44.	Mary Craig	157 High st.	28 "	"
45.	Mrs Craig	"	31 "	"
46.	Wm. "	"	45 "	"

.	Name	Residence	Duration	Result.
47.	Wm.Young	38 Bridge st.	23 days	Recovered
48.	Janet Cowan	Union st.	19 "	"
49.	Hugh Sharpe	37 Arthur st.	31 "	"
50.	Andrew "	"	41 "	"
51.	David Mitchell	Foulford Arms	30 "	"
52.	Thos. Wyllie	30 Hill st.	16 "	"
53.	Jane "	"	19 "	Died
54.	Drummond Wyllie	"	18 "	Recovered
55.	G. Campbell	63 Arthur st.	21 "	Died
56.	Mrs Brown	4 Hill st.	23 "	Recovered
57.	Jas. Nisbet	39 Broad st.	31 "	"
58.	Kath.Drysdale	163 High st.	14 "	"
59.	Mrs "	"	39 "	"
60.	Richard "	"	27 "	"
61.	Robert "	"	20 "	Died
62.	Wm.Campbell	61 Union st.	8 "	Died
63.	Mrs Morris	157 High st.	28 "	Recovered
64.	Mary Gardiner	132 High st.	25 "	"
65.	Mary Gibb	129 Union st.	21 "	"
66.	Maggie "	"	14 "	"
67.	Jeanie "	"	21 "	"
68.	Chas.Horsburgh	15 Union st.	39 "	"
69.	Helen Davidson	100 Union st.	49 "	"
70.	Wm. "	"	17 "	"

	Name	Residence	Duration	Result
71.	Betsy Davidson	100 Union st.	21 days	Recovered
72.	Wm. "	"	28 "	"
73.	John "	"	31 "	"
74.	Wm. " Jr.	92 "	19 "	"
75.	Alex. Watson	138 High st.	16 "	"
76.	John "	"	14 "	"
77.	Francis Canavan	182 "	37 "	"
78.	Helen "	"	29 "	"
79.	Mrs "	"	85 "	"
80.	Peter Smart	84 Bridge st.	28 "	"
81.	Emma "	"	33 "	"
82.	Robt. Easson	Factory rd.	28 "	"

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